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Lignans from *Selaginella doederleinii* and revision of structures of ten lignans*

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Abstract: Five known lignans including three 8,4′-oxyneolignans [(−)-*erythro*-(7′*E*)-4,9-dihydroxy-3,3′,5′-trimethoxy-8,4′-oxyneolign-7′-en-9′-al (**1**), (−)-*erythro*-guaiacylglycerol-*β*-*O*-4′-sinapyl ether (**2**), and (7′*E*)-3,5,3′,5′-tetramethoxy-8,4′-oxyneolign-7′-ene-4,9,9′-triol (**3**)], a benzofuran [(+)-(7*R*,8*S*)-5-methoxydihydrodehydrodiconiferyl alcohol (**4**)], and one furofuran [syringaresinol (**5**)] were isolated from the traditional Chinese medicine *Selaginella doederleinii*. Their structures were elucidated by HRMS and 1D and 2D NMR data. The inhibitory activities of **1**−**5** against thioredoxin reductase (TrxR) were evaluated, and three compounds showed moderate activities with IC_{50} values ranging from 10. 1 to 20. 2 μmol/L. Compounds **1**−**4** were isolated from *S. doederleinii* for the first time. In addition, it was found that the structures of ten known lignans [2,6,2′,6′-tetramethoxy-4,4′-bis(2,3-epoxy-1-hydroxypropyl)biphenyl (Ⅰ), griffilignan A (Ⅱ), 2-hydroxy-3,2′,6′-trimethoxy-4′-(2,3-epoxy-1-hydroxypropyl)-5-(3-hydroxy-1-propenyl)biphenyl (Ⅲ), 2-hydroxy-3,2′-dimethoxy-4′-(2,3-epoxy-1-hydroxypropyl)-5-(3-hydroxy-1-propenyl)biphenyl (Ⅳ), 2,2′-dimethoxy-4-(3-hydroxy-1-propenyl)-4′-(1,2,3-trihydroxypropyl)diphenyl ethers (Ⅴ and Ⅵ), (7′*R*,8′*R*)-2,2′-dimethoxy-4-(3-hydroxyl-propenyl)-4′-(1,2,3-trihydroxypropyl)biphenyl ether (Ⅶ), utiline B (Ⅷ), and rhemaneolignans A and B (Ⅸ and Ⅹ)] were erroneously identified as the types of biphenylneolignans and 4,4′-oxyneolignans due to incorrect elucidation. By comparison of their NMR data with those of model compounds such as some reported synthetic products and the isolates (**1**−**5**), the structures of Ⅰ−Ⅹ were revised as (+)-syringaresinol (**5**), (+)-pinoresinol (**6**), (−)-simulanol (**7**), (−)-dehydrodiconiferyl alcohol (**8**), (−)-*threo*-guaiacylglycerol-*β*-*O*-4′-coniferyl ether (**9**), (+)-*erythro*-guaiacylglycerol-*β*-*O*-4′-coniferyl ether (**10a**), (−)-*erythro*-guaiacylglycerol-*β*-*O*-4′-coniferyl ether (**10b**), (+)-*threo*-guaiacylglycerol-*β*-*O*-4′-sinapyl ether (**11**), (−)-*threo*-methyl 4-*O*-[2-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-1-(hydroxymethyl)ethyl]ferulate (**12**), and (+)-*erythro*-methyl 4-*O*-[2-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-1-(hydroxymethyl)ethyl]ferulate (**13**), respectively. So, it noteworthy that there is no evidence for the existence of the ten lignans in nature, and their revised structures are actually represented as the types of furofurans, benzofurans, and 8,4′-oxyneolignans, respectively.

Key words: Selaginellaceae; *Selaginella doederleinii*; lignan; biphenylneolignan; structural revision

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深绿卷柏中木脂素成分及10个木脂素结构的修订

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摘　要： 从传统中药深绿卷柏（*Selaginella doederleinii*）中分离得到5个已知的木脂素，并利用高分辨质谱及1D和2D NMR数据确定了其结构分别为3个8,4′-氧新木脂素类 [(−)-赤式-(7′*E*)-4,9-二羟基-3,3′,5′-三甲氧基-8,4′-氧新木脂素-7′-烯-9′-醛 (**1**)、(−)-赤式-愈创木基甘油-*β*-*O*-4′-丁香树脂酚醚 (**2**) 和 (7′*E*)-3,5,3′,5′-四甲氧基-8,4′-氧新木脂素-7′-烯-4,9,9′-三醇 (**3**)]，1个苯骈呋喃类 [(+)-(7*R*,8*S*)-5-甲氧二氢去氢二松柏醇 (**4**)] 和1个双四氢呋喃类 [丁香脂素 (**5**)]。硫氧还蛋白氧化还原酶抑制活性评价显示3个化合物具有中等强度活性，其 IC_{50} 值为 10. 1~20. 2 μmol/L。化合物 **1~4** 是首次分离自该植物。另外，发现10个已知木脂素 [2,6,2′,6′-四甲氧基-4,4′-二(1-羟基-2,3-环氧丙基) 联苯 (**Ⅰ**)、2,2′-二甲氧基-4,4′-二 (1-羟基-2,3-环氧丙基) 联苯 (**Ⅱ**)、2-羟基-3,2′,6′-三甲氧基-4′-(1-羟基-2,3-环氧丙基) -5-(3-羟基丙烯基) 联苯 (**Ⅲ**)、2-羟基-3,2′-二甲氧基-4′-(1-羟基-2,3-环氧丙基)-5-(3-羟基丙烯基) 联苯 (**Ⅳ**)、2,2′-二甲氧基-4-(3-羟基丙烯基)-4′-(1,2,3-三羟丙基) 二苯醚 (**Ⅴ**和**Ⅵ**)、(7′*R*,8′*R*)-2,2′-二甲氧基-4-(3-羟丙烯基)-4′-(1,2,3-三羟丙基) 二苯醚 (**Ⅶ**)、野花椒乙素 (**Ⅷ**)、地黄新木甲素 (**Ⅸ**) 和地黄新木乙素 (**Ⅹ**)] 的结构因解析不正确而误定为联苯新木脂素类和4,4′-氧新木脂素类。经过与模型化合物如一些报道的合成物及分离到的化合物（**1~5**）进行NMR数据对比分析后将化合物 **Ⅰ~Ⅹ** 的结构分别修订为(+)-丁香脂素(**5**)、(+)-松脂素(**6**)、(−)-simulanol(**7**)、(−)-去氢二松柏醇 (**8**)、(−)-苏式-愈创木基甘油-*β*-*O*-4′-松柏醇醚(**9**)、(+)-赤式-愈创木基甘油-*β*-*O*-4′-松柏醇醚 (**10a**)、(−)-赤式-愈创木基甘油-*β*-*O*-4′-松柏醇醚(**10b**)、(+)-苏式-愈创木基甘油-*β*-*O*-4′-丁香树脂酚醚 (**11**)、(−)-苏式-4-*O*-[1-羟甲基-2-羟基-2-(3-甲氧基-4-羟苯基) 乙基]阿魏酸甲酯(**12**)和(+)-赤式-4-*O*-[1-羟甲基-2-羟基-2-(3-甲氧基-4-羟苯基) 乙基]阿魏酸甲酯 (**13**)。因此，尚无证据表明自然界中存在这10种木脂素，实际上其修正后的结构分别属于双四氢呋喃类,苯骈呋喃类及8,4′-氧新木脂素类等类型。

关键词： 卷柏科（Selaginellaceae）；深绿卷柏（*Selaginella doederleinii*）；木脂素；联苯新木脂素；结构修订

Selaginella doederleinii Hieron. (Selaginellaceae) is a small evergreen pteridophyte growing throughout south and southwestern China at an altitude of 200−1 000 (−1 400) m[1]. Its whole herbs are used as a traditional Chinese medicine (TCM) for the treatment of sore throat, jaundice, rheumatism, bleeding, and some kinds of cancer[2]. Biflavones are the characteristic chemical constituents of *S. doederleinii*[3]. In addition, previous phytochemical investigation of this plant has led to the isolation of several alkaloids and lignans[4−5]. Most of chemical components from *S. doederleinii* possess various bioactivities such as anticancer, anti−Alzheimer's disease, and cytotoxic properties[6−8].

Recently, the collective evidences suggested that thioredoxin reductase (TrxR) was a potential target for cancer chemotherapy. In our continuing search for natural TrxR inhibitors from TCM[9−10], the EtOH extract of *S. doederleinii* was subjected to chromatographic procedures to afford five lignans (**1−5**) (Fig. 1). The inhibitory activities of these lignans against TrxR were evaluated, and compounds showed moderate activities with IC_{50} values ranging from 10. 1 to 39. 0 μmol/L. However, during the structural elucidation of compounds **1−5** by analyses of their spectroscopic data and comparing with some key synthetic compounds, we found that the structures of ten previously reported compounds (**Ⅰ−Ⅹ**) (Fig. 2) were incorrect. Herein, this report describes details of the isolation, structural elucidation, and inhibitory activities of compounds **1−5** together with the structure revision of **Ⅰ−Ⅹ**.

1　Materials and methods

1. 1　Instruments and reagents

Optical rotations were measured on a PerkinElmer 341 polarimeter, and UV spectra were recorded on a Shimadzu UV−2450 spectrophotometer. IR spectra were determined on a Bruker Tensor 37 infrared spectrophotometer with KBr disks. NMR spectra were measured on a Bruker AM−400 spectrometer at 25 °C. ESIMS and HRESIMS were recorded on a Finnigan LC

Q^{DECA} instrument. A Shimadzu LC-20AT equipped with a SPD-M20A PDA detector was used for HPLC, and a YMC-pack ODS-A column (250 mm × 10 mm, S-5 μm, 12 nm) was used for semipreparative HPLC separation. Silica gel (300-400 mesh, Qingdao Haiyang Chemical Co. Ltd.), reversed-phase C_{18} ($Rp-C_{18}$) silica gel (12 nm, S-50 μm, YMC Co. Ltd), and Sephadex LH-20 gel (Amersham Biosciences) were used for column chromatography (CC). MeOH for HPLC was obtained from BCR International Trading Co., Ltd., and other analytical grade solvents from Shanghai Titan Scientific Co., Ltd. TrxR was purchased from Sigma-Aldrich (St. Louis, USA).

1.2 Plant material

Plants of *S. doederleinii* were collected in March 2013 from Guangdong Province, P. R. China, and were identified by one of the authors (Gui-Hua Tang). A voucher specimen (accession number: 20130303) has been deposited at the School of Pharmaceutical Sciences, Sun Yat-sen University.

1.3 Extraction and isolation

The air-dried and powdered plants of *S. doederleinii* (1.5 kg) were extracted with 95% EtOH (3 L × 3 L) at room temperature to give 150.7 g of crude extract. The extract was suspended in H_2O and successively partitioned with petroleum ether (PE) and EtOAc to yield two corresponding portions. The EtOAc fraction (17.0 g) was subjected to silica gel CC using PE/acetone (2∶1→1∶1→0∶1) to afford three fractions (Ⅰ-Ⅲ). Fr. II was chromatographed over $Rp-C_{18}$ silica gel column with MeOH/H_2O (5∶5→10∶0) to give two fractions (IIa and IIb). Fr. IIa was separated by silica gel CC (CH_2Cl_2/MeOH, 200∶1→100∶1) to give compound **5** (12.0 mg) and four subfractions (IIa1-IIa4). Compound **3** (3.0 mg) was obtained from Fr. IIa2 by semi-preparative HPLC (MeOH/H_2O, 4∶6, 3 mL/min). Fr. IIa3 was purified by a Sephadex LH-20 column ($CHCl_3$/MeOH, 1∶1) to give **4** (5.0 mg). Compounds **1** (2.5 mg) and **2** (7.0 mg) were obtained from Fr. IIa4 by $Rp-C_{18}$ silica gel CC (MeOH/H_2O, 4∶6) and silica gel CC ($CHCl_3$/MeOH, 100∶1).

1.4 Bioactivity assay

The TrxR inhibitory activities of these five isolated lignans were evaluated by the 5,5′-dithiobis(2-nitrobenzoic acid) (DTNB) reduction assay. The procedure for inhibitory assays of TrxR were referred to those we described previously[10]. Briefly, all assays were preformed on 96-well plates with a final volume of 40 μL per well at 25 ℃. 0.3 μL of TrxR (0.04 mmol/L) was mixed with 35.5 μL of reaction buffer (1 mol/L potassium phosphate, pH 7.0; 500 mmol/L EDTA, pH 7.4; 0.48 mmol/L NADPH) and 1 μL of compound at a indicated concentration (3.125, 6.25, 12.5, 25, and 50 μmol/L) in each well. DMSO (2.5%, *V*/*V*) and curcumin were used as vehicle and positive controls, respectively. After mixing for 5 min, the reaction was started by the addition of 3.2 μL of DTNB (final concentration of 5.0 mmol/L). The increase in absorbance at 412 nm ($\varepsilon_{TNB\ 412nm}$ = 13.6 mmol·L^{-1}·cm^{-1}) was monitored in the initial 2 min.

2 Results and discussion

2.1 Structural identification

The whole plants of *S. doederleinii* were extracted with 95% EtOH. After removal of the EtOH by evaporation, the residue was suspended in H_2O and then partitioned successively with petroleum ether and EtOAc. The EtOAc fraction was subjected to column chromatography over silica gel, $Rp-C_{18}$, Sephadex LH-20, and semipreparative HPLC to obtain compounds **1-5**.

The structures **1-5** (Fig. 1) were determined by analysis of their spectroscopic data (1D and 2D NMR data, HRMS, UV, IR, and specific rotation data) and comparison with literature data. All compounds (**1-5**) were known lignans, and **1-4** were isolated from *S. doederleinii* for the first time. (−)-*erythro*-(7′*E*)-4,9-Dihydroxy-3,3′,5′-trimethoxy-8,4′-oxyneolign-7′-en-9′-al (**1**), (−)-*erythro*-guaiacylglycerol-*β*-*O*-4′-sinapyl ether (**2**), and (7′*E*)-3,5,3′,5′-tetramethoxy-8,4′-oxyneolign-7′-ene-4,9,9′-triol (**3**) are represented as the type of 8,4′-oxyneolignan, (+)-(7*R*,8*S*)-5-methoxydihydrodehydrodiconiferyl alcohol (**4**) is the type of benzofuran, and syringaresinol (**5**) belongs to furofuranic lignan.

2.1.1 (−)-*erythro*-(7′*E*)-4,9-Dihydroxy-3,3′,5′-trimethoxy-8,4′-oxyneolign-7′-en-9′-al (1) White amorphous power; [α] −6.7 (*c* 0.1, CH_2Cl_2); UV (MeOH) λ_{max} (log ε) 207 (4.33), 233 (4.22), 323 (4.15)

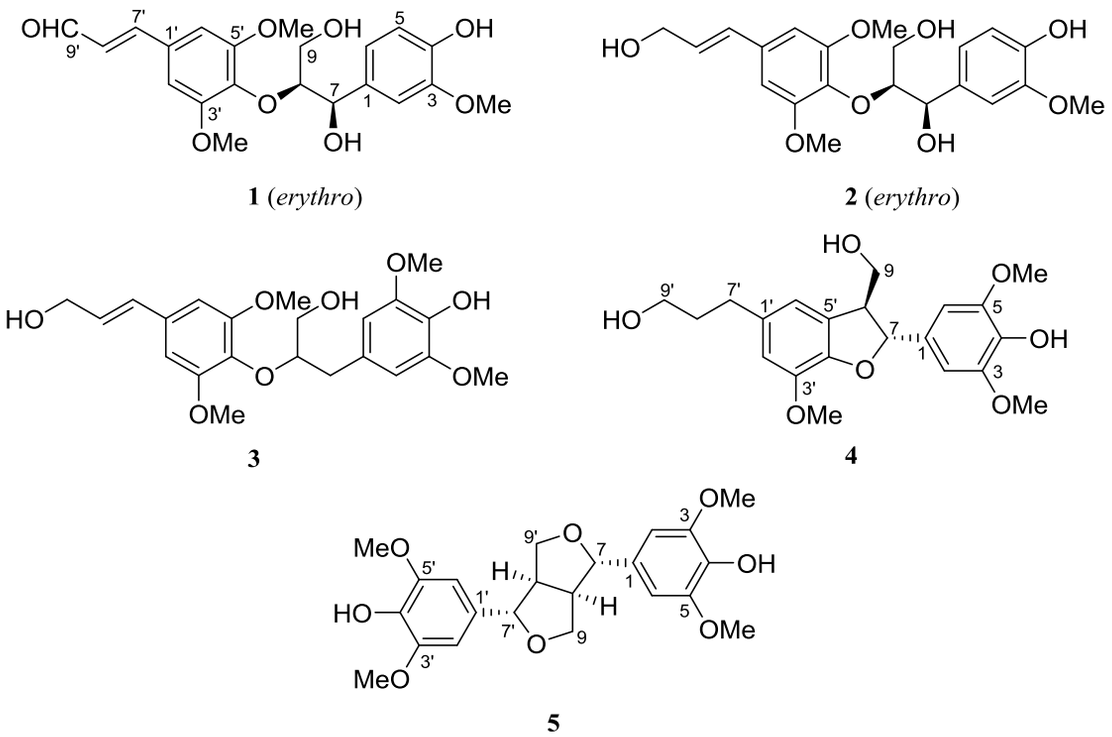

Fig. 1 Structures of compounds **1**–**5** isolated from *S. doederleinii*

nm; IR (KBr) ν_{max} 3 450, 1 668, 1 621, 1 581, 1 517, 1 502, 1 460, 1 425, 1 335, 1 220, 1 125, 1 025 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6. 97 (1H, d, J = 1. 8 Hz, H–2), 6. 87 (1H, d, J = 8. 2 Hz, H–5), 6. 75 (1H, dd, J = 8. 2, 1. 8 Hz, H–6), 5. 02 (1H, d, J = 3. 7 Hz, H–7), 4. 22 (1H, m, H–8), 3. 94 (1H, dd, J = 12. 0, 7. 0 Hz, H–9a), 3. 54 (1H, dd, J = 12. 0, 2. 1 Hz, H–9b), 6. 85 (2H, s, H–2′ and H–6′), 7. 42 (1H, d, J = 15. 9 Hz, H–7′), 6. 67 (1H, dd, J = 15. 9, 7. 6 Hz, H–8′), 9. 71 (1H, d, J = 7. 6 Hz, H–9′), 3. 90 (3H, s, 3–OMe), 3. 93 (6H, s, 3′–OMe and 5′–OMe); ^{13}C NMR data, see Table 1; ESIMS m/z 403 $[M - H]^-$. These data were in consistent with those reported in the literature[11]. Thus, compound **1** was determined as (–) –*erythro*–(7′*E*) –4, 9–dihydroxy–3, 3′, 5′ –trimethoxy–8, 4′ –oxyneolign–7′–en–9′–al.

2. 1. 2 (–) –*erythro*–Guaiacylglycerol–*β*–*O*–4′–sinapyl ether (**2**) White amorphous power; [α] –2. 8 (*c* 0. 6, CH_2Cl_2); UV (MeOH) λ_{max} (log ε) 222 (4. 55), 272 (4. 27) nm; IR (KBr) ν_{max} 3 327, 1 668, 1 588, 1 507, 1 453, 1 233, 1 124, 1 028 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6. 95 (1H, d, J = 1. 5 Hz, H–2), 6. 85 (1H, d, J = 8. 2 Hz, H–5), 6. 75 (1H, dd, J = 8. 2, 1. 5 Hz, H–6), 5. 00 (1H, d, J = 3. 5 Hz, H–7), 4. 13 (1H, m, H–8), 3. 90 (1H, dd, J = 12. 0, 7. 0 Hz, H–9a), 3. 50 (1H, dd, J = 12. 0, 2. 1 Hz, H–9b), 6. 66 (2H, s, H–2′ and H–6′), 6. 56 (1H, d, J = 15. 9 Hz, H–7′), 6. 31 (1H, dt, J = 15. 9, 5. 6 Hz, H–8′), 4. 34 (1H, d, J = 5. 6 Hz, H–9′), 3. 88 (9H, s, 3–OMe, 3′–OMe, and 5′–OMe); ^{13}C NMR data, see Table 1; HRESIMS m/z 429. 151 7 $[M + Na]^+$ (calcd for $C_{21}H_{26}O_8Na$, 429. 152 5). Its NMR and MS data were identical with those reported in the literature[12–13]. Thus, this compound was assigned as (–) –*erythro*–guaiacylglycerol–*β*–*O*–4′–sinapyl ether.

2. 1. 3 (7′*E*) –3, 5, 3′, 5′ –Tetramethoxy–8, 4′ –oxyneolign–7′–ene–4, 9, 9′–triol (**3**) White amorphous power; [α] +17 (*c* 0. 1, CH_2Cl_2); UV (MeOH) λ_{max} (log ε) 209 (4. 38), 271 (3. 85) nm; IR (KBr) ν_{max} 3 500, 1 666, 1 587, 1 505, 1 450, 1 233, 1 122, 1 033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6. 52 (2H, s, H–2 and H–6), 3. 19 (1H, dd, J = 13. 6, 8. 6 Hz, H–7a), 2. 98 (1H, dd, J = 13. 6, 5. 4 Hz, H–7b), 4. 21 (1H, m, H–8), 3. 58 (1H, m, H–9a), 3. 45 (1H, m, H–9b), 6. 63 (2H, s, H–2′ and H–6′), 6. 55 (1H, d, J = 15. 8 Hz, H–7′), 6. 29 (1H, dt, J = 15. 8, 5. 6 Hz, H–8′), 4. 32 (1H, d, J = 5. 6 Hz, H–9′), 3. 87 (6H, s, 3–OMe and 5–OMe), 3. 85 (6H, s, 3′–OMe and 5′–OMe); ^{13}C NMR data, see Table 1; HRESIMS m/z 443. 167 5 $[M + Na]^+$ (calcd for $C_{22}H_{28}O_8$, 443. 168 2). Its NMR and MS data were in

Table 1　^{13}C NMR (100 MHz) data of **1**–**5** isolated from *S. doederleinii* (Recorded in $CDCl_3$)

Position	1	2	3	4	5
1	131.3	131.4	129.5	132.4	132.2
2	108.5	108.6	106.4	103.3	102.9
3	146.8	146.8	147.1	147.3	147.3
4	145.1	145.0	133.4	134.8	134.5
5	119.0	114.3	147.1	147.3	147.3
6	114.4	118.9	106.4	103.3	102.9
7	72.9	72.7	37.9	88.2	86.2
8	87.5	87.3	84.7	54.0	54.5
9	60.7	60.7	62.5	63.9	71.9
1′	130.6	133.6	133.0	135.6	132.2
2′	105.7	103.7	103.9	112.7	102.9
3′	153.9	153.5	153.6	144.3	147.3
4′	137.9	134.8	135.5	146.7	134.5
5′	153.9	153.5	153.6	127.9	147.3
6′	105.7	103.7	103.9	116.1	102.9
7′	152.1	130.7	131.0	32.1	86.2
8′	128.7	129.0	128.6	34.7	54.5
9′	193.4	63.6	63.7	62.4	71.9
3-OMe	56.2	56.1	56.5	56.5	56.5
5-OMe			56.5	56.5	56.5
3′-OMe	56.5	56.3	56.2	56.2	56.5
5′-OMe	56.5	56.3	56.2		56.5

accordance with literature data[14]. Therefore, compound **3** was determined to be (7′*E*)-3,5,3′,5′-tetramethoxy-8,4′-oxyneolign-7′-ene-4,9,9′-triol.

2.1.4　(+)-(7*R*,8*S*)-5-Methoxydihydrodehydrodiconiferyl alcohol (**4**)　White amorphous power; [α] +2.7 (*c* 0.6, CH_2Cl_2); UV (MeOH) λ_{max} (log ε) 212 (4.54), 281 (3.59) nm; IR (KBr) ν_{max} 3 367, 1 607, 1 456, 1 327, 1 218, 1 115, 1 040 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.65 (3H, s, H-2, H-6, and H-2′), 5.52 (1H, d, J = 7.6 Hz, H-7), 3.60 (1H, m, H-8), 3.97 (1H, dd, J = 11.6, 6.0 Hz, H-9a), 3.89 (1H, dd, J = 11.0, 4.9 Hz, H-9b), 6.67 (1H, s, H-6′), 2.67 (2H, m, H-7′), 1.87 (2H, m, H-8′), 3.68 (2H, t, J = 6.3 Hz, H-9′), 3.85 (6H, s, 3-OMe and 5-OMe), 3.88 (3H, s, 3′-OMe); ^{13}C NMR data, see Table 1; HRESIMS *m/z* 413.156 6 $[M + Na]^+$ (calcd for $C_{21}H_{26}O_7Na$, 413.157 6). Its NMR and MS data were identical with those reported in the literature[15]. Thus, the structure of **4** was defined as (+)-(7*R*,8*S*)-5-methoxydihydrodehydrodiconiferyl alcohol.

2.1.5　Syringaresinol (**5**)　White amorphous power; ^1H NMR (400 MHz, $CDCl_3$) δ 5.53 (2H, s, 4-OH and 4′-OH), 6.58 (4H, s, H-2/6 and H-2′/6′), 4.73 (2H, d, J = 4.3 Hz, H-7 and H-7′), 3.09 (2H, m, H-8 and H-8′), 4.28 (2H, m, H-9a and H-9′a), 3.90 (2H, m, H-9b and H-9′b), 3.89 (12H, s, 3/5-OMe and 3′/5′-OMe); ^{13}C NMR data, see Table 1; ESIMS *m/z* 417 $[M - H]^-$. The NMR and MS data were in consistent with those reported in the literature[16]. In addition, the specific optical rotation of the compound was not tested, so its structure was determined to be syringaresinol.

2.2　The results of TrxR activity assay

The inhibitory activities of lignans **1**–**5** against TrxR were tested by the DTNB reduction assay. Compared with the positive control curcumin (IC_{50} = 25.0 μmol/L), compounds **3**, **2**, and **5** represented the most active compounds with IC_{50} values of 10.1, 13.4, and 20.2 μmol/L, respectively, while **4** showed weak activities with IC_{50} values of 39.0 μmol/L and **1** was inactive.

In this part, photochemical investigation of the TCM *S. doederleinii* let the isolation of three 8,4′-oxyneolignans (**1**–**3**), a benzofuran (**4**), and one furofuran (**5**). Compounds **1**–**4** were isolated from *S. doederleinii* for the first time. The inhibitory activities of **1**–**5** against TrxR were evaluated, and compounds **4**–**5** showed moderate activities. These findings suggested that some lignans might be promising structural motif for the development of TrxR inhibitors.

2.3　Structure revision of ten lignans

We found that the structures of ten reported compounds Ⅰ-Ⅹ (Fig. 2) were incorrect and were therefore wrongly considered as the types of biphenylneolignans and 4,4′-oxyneolignans. They were 2,6,2′,6′-tetramethoxy-4, 4′-bis(2, 3-epoxy-1-hydroxypropyl)biphenyl (Ⅰ) from the roots of *Cynanchum atratum*[17] and the stems of *Millettia griffithii*[18], griffilignan A (Ⅱ) from the stems of *Millettia griffithii*[18], 2-hydroxy-3,2′,6′-trimethoxy-4′-(2,3-epoxy-1-hydroxypropyl)-5-(3-hydroxy-1-propenyl)biphenyl (Ⅲ), 2-hydroxy-3,2′-dimethoxy-4′-(2,3-epoxy-1-hydroxypropyl)-5-(3-hydroxy-1-propenyl)biphenyl (Ⅳ), and 2,2′-dime-

thoxy-4- (3-hydroxy-l-propenyl) -4′ - (1, 2, 3-trihydroxypropyl)diphenyl ethers (Ⅴ and Ⅵ) from the woods of *Eurycoma longifolia*[19], (7′*R*,8′*R*)-2,2′-dimethoxy-4-(3-hydroxyl-propenyl)-4′-(1,2,3-trihydroxypropyl)biphenyl ether (Ⅶ) from the aerial parts of *Saussurea pulchella*[16], utiline B (Ⅷ) from the stems of *Zanthoxylum utile*[20], and rhemaneolignans A and B (Ⅸ and Ⅹ) from the roots of *Rehmannia glutinosa*[21], respectively.

By analysis of the ^{13}C NMR data of model compounds such as synthetic and natural products, it could be determined that some fragments of Ⅰ-Ⅹ were incorrect. The characteristic carbon signals for the moiety of hydroxy(oxiran-2-yl)methyl in the synthetic compound, (4-((*R*)-hydroxy((*R*)-oxiran-2-yl)methyl)-2-methoxyphenyl) carbonate (**14**) (Fig. 3), were at δ_C 74. 1 (CH, C-1), 55. 8 (CH, C-2), and 45. 4 (CH_2, C-3)[22]. However, these characteristic carbon signals were not found in the ^{13}C NMR data of Ⅰ-Ⅳ, which indicated that they did not have the hydroxy(oxiran-2-yl) methyl unit. Then the comparison of their 1D NMR data with those of furofurans such as syringaresinol (**5**) and pinoresinol[23] and benzofurans such as (+)-(7*R*, 8*S*) -5-methoxydihydrodehydroconiferyl alcohol (**4**) and simulanol[24] have resulted in their structure revision. Similarly, the characteristic carbon signals (Fig. 3) for the moiety of 1,2,3-trihydroxypropyl in the synthetic compounds, *tert*-butyl (2-methoxy-4- ((1*R*, 2*R*)-1, 2, 3-trihydroxypropyl)phenyl) carbonate (**15**)[22] and *tert*-butyl 1-phenylpropane-1, 2, 3-triol (**16**)[25] (Fig. 3), were quite different from those for the same fragments in Ⅴ-Ⅹ. Especially, the present of the downfield-shifted ^{13}C NMR chemical shifts of an oxygenated methine [δ_C ca. 86. 5 (CH)] in Ⅴ-Ⅹ suggested that there must be a highly electrophilic *O*-substituent attached to this carbon instead of an OH. Therefore, the structure revision of Ⅴ-Ⅹ were achieved by comparative analysis of their NMR data with **1** and **2** as well as other 8,4′-oxyneolignans.

On the basis of spectroscopic data including NMR and specific rotation data comparison with the isolates (**1**-**5**)(Fig. 1) in this study together with some synthetic compounds and natural products, compounds Ⅰ-Ⅹ were revised to be (+)-syringaresinol (**5**)[16,26-27], (+)-pinoresinol (**6**)[23,26,28-29], (-)-simulanol (**7**)[24,30], (-)-dehydrodiconiferyl alcohol (**8**)[23], (-)-*threo*-guaiacylglycerol-*β*-*O*-4′-coniferyl ether (**9**)[12,31-32], (+)-*erythro*-guaiacylglycerol-*β*-*O*-4′-coniferyl ether (**10a**)[12, 31, 32], (-)-*erythro*-guaiacylglycerol-*β*-*O*-4′-coniferyl ether (**10b**)[32], (+)-*threo*-guaiacylglycerol-*β*-*O*-4′-sinapyl ether (**11**)[12], (-)-*threo*-methyl 4-*O*-[2-hydroxy-2-(4-hydroxy-3-methoxyphenyl) -1- (hydroxymethyl)ethyl]ferulate (**12**)[33], and (+)-*erythro*-methyl 4-*O*-[2-hydroxy-2-(4-hydroxy-3-methoxyphenyl)-1-(hydroxymethyl)ethyl]ferulate (**13**)[33], respectively (Fig. 2). The revised structures are actually the types of furofurans (**5** and **6**), benzofurans (**7** and **8**), and 8,4′-oxyneolignans (**9**-**13**), rather than biphenylneolignans (Ⅰ and Ⅱ) and 4,4′-oxyneolignans (Ⅲ-Ⅹ). Thus far, there is no evidence to support the existence of Ⅰ-Ⅹ in nature.

2. 3. 1 (+)-Syringaresinol (**5**) Colorless needles; $[\alpha]_D$ +75. 0; ^{1}H NMR (400 MHz, $CDCl_3$) δ 5. 54 (2H, s, 4-OH and 4′-OH), 6. 57 (4H, s, H-2/6 and H-2′/6′), 4. 78 (2H, d, J = 7. 0 Hz (The reported data with differences: lit.[26] 7. 0 Hz, lit.[16,27] 4. 3 Hz), H-7 and H-7′), 3. 09 (2H, m, H-8 and H-8′), 4. 26 (2H, m, H-9a and H-9′a), 3. 89 (2H, m, H-9b and 9′b), 3. 90 (12H, s, 3/5-OMe and 3′/5′-OMe); ^{13}C NMR data, see Table 2. All data were from the reported for 2,6,2′,6′-tetramethoxy-4, 4′-bis(2, 3-epoxy-1-hydroxypropyl)biphenyl (Ⅰ)[17], and the 1D NMR assignments of its revised structure were completed on the basis of the comparison of its NMR data with that of the correct compound[16, 26-27].

2. 3. 2 (+)-Pinoresinol (**6**) Pale yellow oil;$[\alpha]_D$ +63. 2; ^{1}H NMR (400 MHz, CD_3OD) δ 6. 94 (2H, d, J = 1. 6 Hz, H-2 and H-2′), 6. 76 (2H, d, J = 8. 0 Hz, H-5 and H-5′), 6. 80 (2H, dd, J = 8. 0, 1. 6 Hz, H-6 and H-6′), 4. 70 (2H, d, J = 7. 2 Hz (The reported data with differences: lit.[26, 28] 5. 0 Hz, lit.[23, 29] 4. 4 Hz), H-7 and H-7′), 3. 12 (2H, ddd, J = 7. 2, 6. 8, 3. 2 Hz, H-8 and H-8′), 4. 22 (2H, dd, J = 9. 2, 6. 8 Hz, H-9a and H-9′a), 3. 82 (2H, dd, J = 9. 2, 3. 2 Hz, H-9b and H-9′b), 3. 84 (6H, s, 3-OMe and 3′-OMe); ^{13}C NMR data, see Table 2. The above data were from the reported for griffilignan A (Ⅱ)[18], and the 1D NMR assignments of its revised structure were completed by comparing of its NMR data with that of the correct structure[23,26,28-29].

2. 3. 3 (-)-Simulanol (**7**) Yellow needles;$[\alpha]_D$ -2. 6;

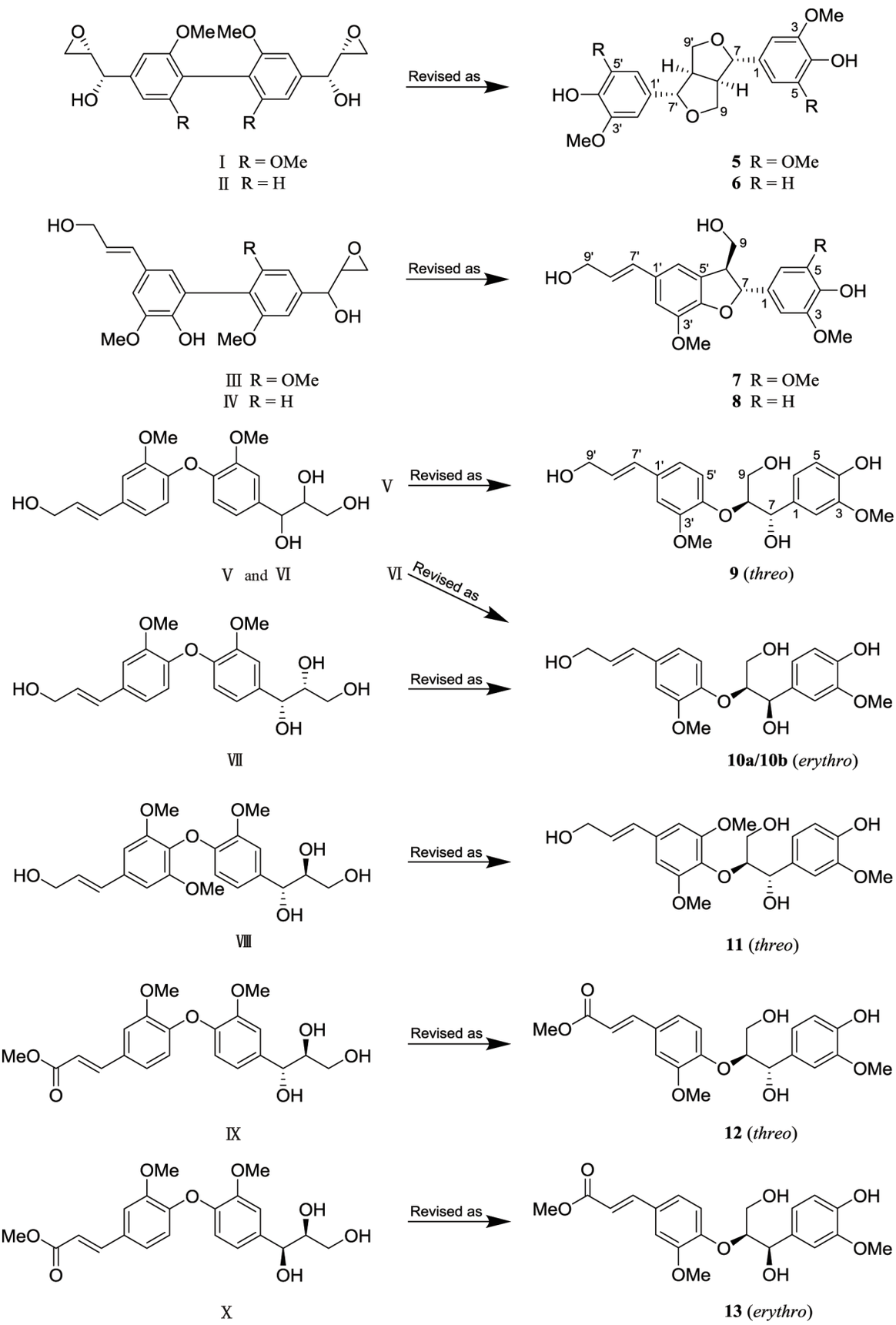

Fig. 2　Structures of Ⅰ－Ⅹ reported previously in literatures and their revised structures (**5** － **13**)

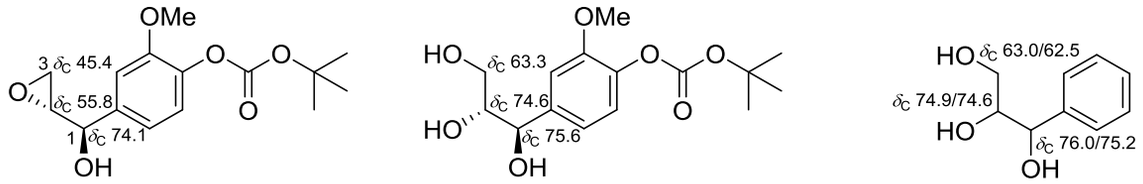

Fig. 3 Structures of the reported synthetic compounds **14–16**

Table 2 ^{13}C NMR data of compounds **5–13**

Position	**5**[1)]	**6**[2)]	**7**[3)]	**8**[3)]	**9**[3)]	**10a**[3)]	**10b**[4)]	**11**[5)]	**12**[6)]	**13**[7)]
1	132. 0	133. 8	132. 5	133. 5	132. 0	131. 9	132. 0	133. 9	134. 0	132. 9
2	102. 7	111. 0	104. 8	110. 8	110. 8	110. 9	110. 1	112. 2	112. 0	111. 0
3	147. 1	149. 2	149. 3	148. 8	151. 1	151. 2	150. 6	149. 3	148. 7	147. 0
4	134. 3	147. 4	137. 7	148. 2	149. 2	148. 7	148. 1	147. 7	147. 1	145. 5
5	147. 1	116. 2	149. 3	116. 5	117. 9	117. 8	117. 8	116. 3	115. 6	114. 6
6	102. 7	120. 1	104. 8	119. 7	120. 0	119. 9	119. 5	121. 5	121. 2	119. 0
7	86. 0	87. 5	88. 9	88. 7	73. 4	73. 6	72. 8	75. 1	74. 1	76. 0
8	54. 3	55. 4	54. 7	54. 7	87. 3	86. 2	86. 2	89. 7	85. 5	83. 8
9	71. 8	72. 6	64. 1	64. 2	61. 7	61. 7	60. 7	64. 1	64. 2	60. 1
1′	132. 0	133. 8	131. 9	131. 8	134. 0	134. 5	132. 6	135. 4	129. 5	126. 7
2′	102. 7	111. 0	111. 7	111. 7	111. 9	112. 0	110. 6	105. 6	112. 4	111. 2
3′	147. 1	149. 2	144. 9	144. 9	148. 4	148. 4	147. 6	154. 8	151. 8	150. 8
4′	134. 3	147. 4	148. 8	148. 8	147. 5	147. 4	146. 0	137. 4	151. 8	149. 5
5′	147. 1	116. 2	130. 6	130. 6	116. 0	116. 0	114. 0	154. 8	117. 6	114. 4
6′	102. 7	120. 1	115. 9	115. 9	120. 6	120. 6	119. 6	105. 6	123. 5	122. 6
7′	86. 0	87. 5	129. 9	130. 0	129. 4	129. 4	127. 4	131. 8	146. 3	144. 7
8′	54. 3	55. 4	129. 0	128. 9	129. 8	129. 7	130. 2	130. 4	116. 5	111. 2
9′	71. 8	72. 6	63. 0	63. 0	62. 9	62. 9	62. 5	64. 1	169. 5	167. 0
3–OMe	56. 3	56. 5	56. 3	55. 8	55. 9	55. 9	55. 9	56. 8	56. 3	55. 4
5–OMe	56. 3		56. 3							
3′–OMe	56. 3	56. 5	56. 2	56. 2	55. 8	55. 8	55. 8	57. 1	56. 6	55. 7
5′–OMe	56. 3							57. 1		
9′–OMe									52. 0	51. 2

1) Data (recorded in $CDCl_3$) from literature[17]; 2) Data (recorded in CD_3OD) from literature[18]; 3) Data (recorded in pyridine–d_5) from literature[19]; 4) Data (recorded in CD_3OD) from literature[16]; 5) Data (recorded in CD_3OD) from literature[20]; 6) Data (recorded in CD_3OD) from literature[21]; 7) Data (recorded in DMSO–d_6) from literature[21] .

^{1}H NMR (400 MHz, pyridine–d_5) δ 7. 10 (2H, s, H–2 and H–6), 6. 11 (1H, d, J = 7. 0 Hz, H–7), 4. 08 (1H, br. ddd, J = 6. 2, 6. 2, 6. 2 Hz, H–8), 4. 31 (1H, dd, J = 10. 8, 5. 3 Hz, H–9a), 4. 26 (1H, dd, J = 10. 8, 6. 6 Hz, H–9b), 7. 15 (1H, s, H–2′), 7. 33 (1H, s, H–6′), 6. 91 (1H, d, J = 15. 9 Hz, H–7′), 6. 57 (1H, dt, J = 15. 9, 5. 3 Hz, H–8′), 4. 59 (1H, d, J = 5. 3 Hz, H–9′), 3. 73 (6H, s, 3–OMe and 5–OMe), 3. 86 (3H, s, 3′–OMe); ^{13}C NMR data, see Table 2. The above information were from the reported for 2–hydroxy–3,2′,6′–trimethoxy–4′–(2, 3–epoxy–1–hydroxypropyl) –5– (3–hydroxy–l–propenyl)biphenyl (Ⅲ)[19], and the 1D NMR assignments of its revised structure were completed by comparing of its NMR data with that of the correct

structure[24,30].

2.3.4　(−)−Dehydrodiconiferyl alcohol (**8**)　Yellow needles; $[\alpha]_D$ −9.7; ^{1}H NMR (400 MHz, pyridine−d_5) δ 7.32 (1H, s, H−2), 7.22 (2H, overlapped, H−5 and H−6), 6.08 (1H, d, J = 6.7 Hz, H−7), 3.97 (1H, br. ddd, J = 6.2, 6.2, 6.2 Hz, H−8), 4.27 (1H, dd, J = 10.7, 5.5 Hz, H−9a), 4.26 (1H, dd, J = 10.7, 6.7 Hz, H−9b), 7.14 (1H, s, H−2′), 7.32 (1H, s, H−6′), 6.91 (1H, d, J = 15.9 Hz, H−7′), 6.57 (1H, dt, J = 15.9, 5.3 Hz, H−8′), 4.59 (1H, d, J = 5.3 Hz, H−9′), 3.66 (3H, s, 3−OMe), 3.28 (3H, s, 3′−OMe); ^{13}C NMR data, see Table 2. All data were from the reported for 2−hydroxy−3,2′−dimethoxy−4′−(2,3−epoxy−1−hydroxypropyl)−5−(3−hydroxy−1−propenyl)biphenyl (Ⅳ)[19], and the 1D NMR assignments of its revised structure were completed on the basis of the comparison of its NMR data with that of the correct compound[23].

2.3.5　(−)−*threo*−Guaiacylglycerol−*β*−*O*−4′−coniferyl ether (**9**)　Yellow needles; $[\alpha]_D$ −2.5; ^{1}H NMR (400 MHz, pyridine−d_5) δ 7.19 (1H, d, J = 1.2 Hz, H−2), 7.50 (1H, d, J = 8.3 Hz, H−5), 7.07 (1H, dd, J = 8.3, 1.2 Hz, H−6), 5.60 (1H, d, J = 5.7 Hz, H−7), 4.98 (1H, br. ddd, J = 5.6, 5.6, 5.6 Hz, H−8), 4.40 (1H, dd, J = 11.8, 3.6 Hz, H−9a), 4.11 (1H, dd, J = 11.8, 5.7 Hz, H−9b), 7.59 (1H, d, J = 1.7 Hz, H−2′), 7.27 (1H, d, J = 7.8 Hz, H−5′), 7.42 (1H, dd, J = 7.8, 1.7 Hz, H−6′), 6.89 (1H, d, J = 15.9 Hz, H−7′), 6.58 (1H, dt, J = 15.9, 5.2 Hz, H−8′), 4.58 (1H, d, J = 5.2 Hz, H−9′), 3.75 (3H, s, 3−OMe), 3.78 (3H, s, 3′−OMe); ^{13}C NMR data, see Table 1. The above information were from the reported for 2,2′−dimethoxy−4−(3−hydroxy−l−propenyl)−4′−(1,2,3−trihydroxypropyl)diphenyl ether (Ⅴ)[19], and the 1D NMR assignments of its revised structure were completed by comparing of its NMR data with that of the correct structure[12,31,32].

2.3.6　(+)−*erythro*−Guaiacylglycerol−*β*−*O*−4′−coniferyl ether (**10a**)　Yellow needles; $[\alpha]_D$ +1.3; ^{1}H NMR (400 MHz, pyridine−d_5) δ 7.14 (1H, d, J = 1.9 Hz, H−2), 7.37 (1H, d, J = 8.3 Hz, H−5), 7.04 (1H, dd, J = 8.3, 1.9 Hz, H−6), 5.60 (1H, d, J = 5.1 Hz, H−7), 5.03 (1H, br. ddd, J = 4.9, 4.9, 4.9 Hz, H−8), 4.55 (1H, dd, J = 11.8, 3.8 Hz, H−9a), 4.41 (1H, dd, J = 11.8, 5.4 Hz, H−9b), 7.59 (1H, d, J = 2.0 Hz, H−2′), 7.24 (1H, d, J = 8.0 Hz, H−5′), 7.38 (1H, dd, J = 8.0, 2.0 Hz, H−6′), 6.85 (1H, d, J = 15.9 Hz, H−7′), 6.55 (1H, dt, J = 15.9, 5.3 Hz, H−8′), 4.56 (1H, d, J = 5.3 Hz, H−9′), 3.72 (3H, s, 3−OMe), 3.74 (3H, s, 3′−OMe); ^{13}C NMR data, see Table 2. The above data were from the reported for 2,2′−dimethoxy−4−(3−hydroxy−l−propenyl)−4′−(1,2,3−trihydroxypropyl)diphenyl ethers (Ⅵ)[19], and the 1D NMR assignments of its revised structure were completed by comparing of its NMR data with that of the correct structure[12,31,32].

2.3.7　(−)−*erythro*−Guaiacylglycerol−*β*−*O*−4′−coniferyl ether (**10b**)　Colorless oil; $[\alpha]_D$ −8.0; ^{1}H NMR (500 MHz, CD_3OD) δ 7.04 (1H, d, J = 1.8 Hz, H−2), 6.77 (1H, d, J = 8.0 Hz, H−5), 6.88 (1H, dd, J = 8.0, 1.8 Hz, H−6), 4.90 (1H, d, J = 5.0 Hz, H−7), 4.32 (1H, q, J = 5.0 Hz, H−8), 3.79 (1H, dd, J = 12.0, 4.0 Hz, H−9a), 3.50 (1H, dd, J = 12.0, 5.0 Hz, H−9b), 7.07 (1H, d, J = 2.0 Hz, H−2′), 7.01 (1H, d, J = 8.0 Hz, H−5′), 7.38 (1H, dd, J = 8.0, 2.0 Hz, H−6′), 6.56 (1H, d, J = 15.9 Hz, H−7′), 6.30 (1H, dt, J = 15.9, 5.7 Hz, H−8′), 4.56 (1H, d, J = 5.7 Hz, H−9′), 3.83 (3H, s, 3−OMe), 3.89 (3H, s, 3′−OMe); ^{13}C NMR data, see Table 2. The above information were from the reported for (7′*R*,8′*R*)−2,2′dimethoxy−4−(3−hydroxyl−propenyl) −4′ − (1, 2, 3−trihydroxypropyl)biphenyl ether (Ⅶ)[16], and the 1D NMR assignments of its revised structure were completed by comparing of its NMR data with that of the correct structure[32].

2.3.8　(+)−*threo*−Guaiacylglycerol−*β*−*O*−4′−sinapyl ether (**11**)　Colorless oil; $[\alpha]_D$ +6.6; ^{1}H NMR (400 MHz, CD_3OD) δ 7.04 (1H, d, J = 1.2 Hz, H−2), 6.79 (1H, d, J = 8.0 Hz, H−5), 6.89 (1H, dd, J = 8.0, 1.6 Hz, H−6), 5.01 (1H, d, J = 7.2 Hz, H−7), 4.00−4.06 (1H, m, H−8), 3.77 (1H, dd, J = 12.0, 4.0 Hz, H−9a), 3.30−3.34 (1H, m, H−9b), 6.77 (2H, d, J = 1.7 Hz, H−2′ and H−6′), 6.57 (1H, d, J = 15.6 Hz, H−7′), 6.36 (1H, dt, J = 15.6, 5.6 Hz, H−8′), 4.24 (1H, d, J = 5.6 Hz, H−9′), 3.84 (3H, s, 3−OMe), 3.90 (3H, s, 3′−OMe and 5′−OMe); ^{13}C NMR data, see Table 2. All data were from the reported for utiline B (Ⅷ)[20], and the 1D NMR assignments of its revised structure were completed on the basis of the comparison of its NMR data with that of the correct compound[12].

2.3.9　(−)−*threo*−Methyl 4−*O*−[2−hydroxy−2−(4−hy-

droxy-3-methoxyphenyl) -1- (hydroxymethyl)ethyl]ferulate (**12**) Colorless amorphous power; $[\alpha]_D$ - 4. 2; ^{1}H NMR (500 MHz, CD_3OD) δ 7. 02 (1H, d, J = 1. 2 Hz, H-2), 6. 70 (1H, d, J = 8. 0 Hz, H-5), 6. 83 (1H, dd, J = 8. 0, 2. 0 Hz, H-6), 4. 81 (1H, d, J = 6. 0 Hz, H-7), 4. 48 (1H, m, H-8), 3. 83 (1H, m, H-9a), 3. 76 (1H, m, H-9b), 7. 15 (1H, d, J = 2. 0 Hz, H-2′), 6. 95 (1H, d, J = 8. 5 Hz, H-5′), 7. 06 (1H, dd, J = 8. 5, 2. 0 Hz, H-6′), 7. 59 (1H, d, J = 16. 0 Hz, H-7′), 6. 38 (1H, d, J = 16. 0 Hz, H-8′), 3. 77 (3H, s, 3-OMe), 3. 81 (3H, s, 3′-OMe), 3. 76 (3H, s, 9′-OMe); ^{13}C NMR data, see Table 2. The above data were from the reported for rhemaneolignan A (**IX**)[21], and the 1D NMR assignments of its revised structure were completed by comparing of its NMR data with that of the correct structure[33].

2. 3. 10 (+)-*erythro*-Methyl 4-*O*-[2-hydroxy-2-(4-hydroxy-3-methoxyphenyl) -1- (hydroxymethyl)ethyl] ferulate (**13**) Colorless amorphous power; $[\alpha]_D$ +1. 8; ^{1}H NMR (500 MHz, DMSO-d_6) δ 6. 95 (1H, d, J = 2. 0 Hz, H-2), 6. 66 (1H, d, J = 8. 0 Hz, H-5), 6. 74 (1H, dd, J = 8. 0, 2. 0 Hz, H-6), 4. 68 (1H, d, J = 4. 0 Hz, H-7), 4. 37 (1H, m, H-8), 3. 56 (1H, m, H-9a), 3. 23 (1H, m, H-9b), 7. 32 (1H, d, J = 2. 0 Hz, H-2′), 7. 04 (1H, d, J = 8. 0 Hz, H-5′), 7. 18 (1H, dd, J = 8. 0, 2. 0 Hz, H-6′), 7. 51 (1H, d, J = 16. 0 Hz, H-7′), 6. 52 (1H, d, J = 16. 0 Hz, H-8′), 3. 71 (3H, s, 3-OMe), 3. 80 (3H, s, 3′-OMe), 3. 69 (3H, s, 9′-OMe); ^{13}C NMR data, see Table 2. All data were from the reported for rhemaneolignan B (**X**)[21], and the 1D NMR assignments of its revised structure were completed on the basis of the comparison of its NMR data with that of the correct compound[33].

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